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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/038,717	01/08/2002	Yuki Wakabayashi	NITT.0052	8912

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EXAMINER	
FREDMAN, JEFFREY NORMAN	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 09/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/038,717	WAKABAYASHI ET AL.	
	Examiner	Art Unit	
	Jeffrey Fredman	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 8-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

Status

1. Claims 1-4 and 8-14 are pending.

Claims 1-4 and 8-14 are rejected.

Claim Rejections - 35 USC § 112

2. The rejection of claims 1-4 and 6-14 are rejected under 35 U.S.C. 112, second paragraph, is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4 and 8-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Nyren et al (WO 98/13523).

Nyren teaches a method of analysis of DNA sequence of claim 1 (see abstract), comprising the steps of:

(a) treating reagent solutions with apyrase (see page 7, paragraph 2, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix") and then degrading, by apyrase, adenosine s'-triphosphate contained in the reagent (see page 7, paragraph 2);

(b) removing or inactivating the pyrophosphates and/or the apyrase in the reagent after the degrading step (see page 7, where Nyren teaches removal of the

apyrase using magnetic beads "The immobilised enzyme may then be removed prior to the chain extension/detection");

(c) conducting the extension reaction (see pages 13 to 15, where Nyren teaches that the mixture may then be extended); and

(d) detecting pyrophosphoric acid generated by the extension reaction after the removing or inactivating step (see pages 13-15 and page 25 for methods of detection using luciferase).

Wherein the reagent solution does not contain the DNA primer, target nucleic acid and the reagent (see page 7, paragraph 2, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix", where Nyren expressly teaches removal of the ATP from the reagent solutions prior to addition to the reaction mix).

With regard to claim 2, Nyren teaches immobilization of the apyrase on a solid (see page 7).

With regard to claim 3, Nyren teaches detection of chemiluminescence where solutions of different nucleotides are present, since the nucleotides are added sequentially one by one, therefore when all four nucleotides are used (as in figures 1 and 3, for example), the reagent solutions discussed at page 7, paragraph 2 would include each different nucleotide.

With regard to claim 4, Nyren teaches the conversion using adenosine 5' phosphosulfate and ATP sulfurylase (see page 25) as well as the detection using chemiluminescence using ATP (see page 25).

With regard to claim 6, Nyren teaches adding apyrase to the reagent solutions (see page 7, paragraph 2, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix").

With regard to claim 7, Nyren teaches removing the pyrophosphatase/apyrase (see page 7, where Nyren teaches removal of the apyrase using magnetic beads "The immobilised enzyme may then be removed prior to the chain extension/detection").

With regard to claim 8, Nyren teaches the apyrase is immobilized on a solid (see page 7).

With regard to claim 9, Nyren teaches detection of SNPs (see page 12, last paragraph to page 13, first paragraph).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (WO 98/13523) in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Nyren et al (WO 98/13523) teaches a method of claims 1-4 and 6-9 as discussed above. Nyren et al (WO 98/13523) does not teach the use of mismatched primers.

Ishikawa teaches that putting mismatches in primers near the 3' termini increases the specificity of amplification (abstract and page 316, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the sequencing method of Nyren et al (WO 98/13523) to use primers which have been modified to improve specificity as taught by Ishikawa since Ishikawa states "the introduction of an additional one-base mismatch is a simple and useful way to improve the specificity (page 316, column 2)". An ordinary practitioner would have been motivated to modify the primers of Nyren by creating mismatches near the 3' end in order to improve the specificity of the single base extension reaction, thereby improving the quality of the assay and reducing the number of false negative and false positives which would otherwise occur, thereby increasing the specificity of the sequencing reaction.

8. Claims 1-4, 8-9, 11, 12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (WO 98/13523) in view of Nyren et al (WO 98/28440).

Nyren et al (WO 98/13523) teaches a method of analysis of DNA sequence of claim 1 (see abstract), comprising the steps of:

(a) treating reagent solutions with apyrase (see page 7, paragraph 2, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix") and then degrading, by apyrase, adenosine s'-triphosphate contained in the reagent (see page 7, paragraph 2);

(b) removing or inactivating the pyrophosphates and/or the apyrase in the reagent after the degrading step (see page 7, where Nyren et al (WO 98/13523) teaches removal of the apyrase using magnetic beads "The immobilised enzyme may then be removed prior to the chain extension/detection");

(c) conducting the extension reaction (see pages 13 to 15, where Nyren et al (WO 98/13523) teaches that the mixture may then be extended); and

(d) detecting pyrophosphoric acid generated by the extension reaction after the removing or inactivating step (see pages 13-15 and page 25 for methods of detection using luciferase).

Wherein the reagent solution does not contain the DNA primer, target nucleic acid and the reagent (see page 7, paragraph 2, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix", where Nyren et al (WO 98/13523) expressly teaches removal of the ATP from the reagent solutions prior to addition to the reaction mix).

With regard to claim 2, Nyren et al (WO 98/13523) teaches immobilization of the apyrase on a solid (see page 7).

With regard to claim 3, Nyren et al (WO 98/13523) teaches detection of chemiluminescence where solutions of different nucleotides are present, since the nucleotides are added sequentially one by one, therefore when all four nucleotides are used (as in figures 1 and 3, for example), the reagent solutions discussed at page 7, paragraph 2 would include each different nucleotide.

With regard to claim 4, Nyren et al (WO 98/13523) teaches the conversion using adenosine 5' phosphosulfate and ATP sulfurylase (see page 25) as well as the detection using chemiluminescence using ATP (see page 25).

With regard to claim 6, Nyren et al (WO 98/13523) teaches adding apyrase to the reagent solutions (see page 7, paragraph 2, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix").

With regard to claim 7, Nyren et al (WO 98/13523) teaches removing the pyrophosphatase/apyrase (see page 7, where Nyren et al (WO 98/13523) teaches removal of the apyrase using magnetic beads "The immobilised enzyme may then be removed prior to the chain extension/detection").

With regard to claim 8, Nyren et al (WO 98/13523) teaches the apyrase is immobilized on a solid (see page 7).

With regard to claim 9, Nyren et al (WO 98/13523) teaches detection of SNPs (see page 12, last paragraph to page 13, first paragraph).

Nyren et al (WO 98/13523) does not teach the use of pyrophoshatase to remove pyrophosphoric acid.

Nyren et al (WO 98/28440) teaches a method of analysis of DNA sequence of claim 1 (see abstract), comprising the steps of:

(a) treating reagent solutions with pyrophosphatase (see page 19, lines 2-9) and then degrading, by pyrophosphatase, pyrophosphoric acid contained in a reagent used for extension reaction of a DNA primer hybridized to a target nucleic acid through a complementary binding, and/or degrading, by apyrase, adenosine s'-triphosphate contained in the reagent (see page 6, where Nyren et al (WO 98/28440) teaches that DNA, which is generated by extending a DNA primer hybridized to a target nucleic acid, is treated with an immobilized nucleotide degrading enzyme, and Nyren et al (WO 98/28440) teaches that apyrase is the preferred enzyme at page 4);

(b) removing or inactivating the pyrophosphates and/or the apyrase in the reagent after the degrading step (see page 6, where Nyren et al (WO 98/28440) inactivates the enzymatically treated sample by removing the immobilized enzyme from the reaction mixture);

(c) conducting the extension reaction (see page 6, where Nyren et al (WO 98/28440) teaches that the mixture may then be extended); and

(d) detecting pyrophosphoric acid generated by the extension reaction after the removing or inactivating step (see page 6 and see page 7 for methods of detection using luciferase).

As a particular comment, Nyren et al (WO 98/28440) teaches addition of a pyrophosphatase in reagent solutions to minimize PPi contamination (see page 19).

With regard to claim 2, Nyren et al (WO 98/28440) teaches immobilization of the apyrase (see page 6).

With regard to claim 3, Nyren et al (WO 98/28440) teaches detection of chemiluminescence where solutions of different nucleotides are present, since the nucleotides are added sequentially one by one, therefore when all four nucleotides are used (as in figure 3, for example), the method of claim 6 would involve adding a pyrophosphatase to a sequence with each different nucleotide.

With regard to claim 4, Nyren et al (WO 98/28440) teaches the conversion using adenosine 5' phosphosulfate and ATP sulfurylase (see pages 7 and 8) as well as the detection using chemiluminescence using ATP (see page 8).

With regard to claim 6, Nyren et al (WO 98/28440) teaches adding pyrophosphatase to the solution with the DNA polymerase (see page 6, where the enzyme is added to the extension reaction which comprises at least a DNA polymerase, as well as ll the other listed components as discussed at pages 7 and 8).

With regard to claim 7, Nyren et al (WO 98/28440) teaches removing the pyrophosphatase/apyrase (see page 6).

With regard to claim 8, Nyren et al (WO 98/28440) teaches the apyrase is immobilized on a solid (see page 6).

With regard to claim 9, Nyren et al (WO 98/28440) teaches detection of SNPs (see page 1, last sentence to page 2, first sentence and pages 27-28).

With regard to claims 11-12, Nyren et al (WO 98/28440) teaches addition of pyrophosphatase to each extension step (see page 6), which will include addition to

each of the four dNTPs used in the sequencing reaction since the reaction sequentially uses all four dNTPs (see figure 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to remove all of the contaminants from the reagent solutions prior to addition to the reaction mix since Nyren et al (WO 98/13523) states, "It may be advantageous therefore, to remove ATP from reagent solutions prior to addition to the reaction mix (page 7, paragraph 2)" and since Nyren et al (WO 98/28440) teaches "In carrying out the method of the invention, any possible contamination of the reagents e.g. the NTP solutions, by PPi is undesirable and may readily be avoided by including a pyrophosphatase, preferably in low amounts in the reagent solutions (see page 19, paragraph 1)." Therefore, an ordinary practitioner would have been motivated by each of the Nyren prior art references to use pyrophosphatase and apyrase to remove ATP and Ppi from the reagent solutions in order improve reaction efficiency and minimize contamination, thereby maximizing real signal. Further, Nyren et al (WO 98/13523) expressly motivates removal of the enzymes prior to addition to the reaction mix, noting "The immobilised enzyme may then be removed prior to the chain extension/detectoin (see page 7, paragraph 2)." This leads to the conclusion that an ordinary practitioner would have been motivated to remove all the contaminants from the reagent solutions prior to the reacton mixture being formed, and removed the enzymes after treatment, in order to maximize reaction efficiency and minimize contaminating signal.

To preemptively address the argument that the concluding statement that the removal steps have not generally been found to be necessary as a "teaching away", it is noted that MPEP 2123 states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi,169 USPQ 423 (CCPA 1971)." MPEP 2123 also states " A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. Merck & Co. v. Biocraft Laboratories , 10 USPQ2d 1843 (Fed. Cir. 1989)." It is clear that simply because Nyren et al (WO 98/13523) suggested that sometimes this step is not be necessary, this embodiment does not teach away from the use of this expressly taught contamination removal step. In fact, the mere inclusion of the teaching into the Nyren et al (WO 98/13523) disclosure indicates that this may be desirable under some circumstances.

9. Claims 10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyren et al (WO 98/13523) in view of Nyren et al (WO 98/28440) and further in view of Ishikawa et al (Human Immunology (1995) 42:315-318).

Nyren et al (WO 98/13523) in view of Nyren et al (WO 98/28440) teach a method of claims 1-4, 6-9, 11, 12 and 14 as discussed above. Nyren et al (WO 98/13523) in view of Nyren et al (WO 98/28440) do not teach the use of mismatched primers.

Ishikawa teaches that putting mismatches in primers near the 3' termini increases the specificity of amplification (abstract and page 316, column 2).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to modify the sequencing method of Nyren et al (WO 98/13523) in view of Nyren et al (WO 98/28440) to use primers which have been modified to improve specificity as taught by Ishikawa since Ishikawa states "the introduction of an additional one-base mismatch is a simple and useful way to improve the specificity (page 316, column 2)". An ordinary practitioner would have been motivated to modify the primers of Nyren et al (WO 98/13523) in view of Nyren et al (WO 98/28440) by creating mismatches near the 3' end in order to improve the specificity of the single base extension reaction, thereby improving the quality of the assay and reducing the number of false negative and false positives which would otherwise occur, thereby increasing the specificity of the sequencing reaction.

Response to Arguments

10. Applicant's arguments filed August 12, 2005 have been fully considered but they are not persuasive.

Applicant argues that Nyren (WO 98/13523) only teaches removal of ATP and not removal of Ppi. This argument is not commensurate in scope with the claims. Claim 1, for example, expressly states that the substrate solution may be treated with either pyrophosphatase or apyrase, in the alternative, and is not limited to the removal of Ppi. Applicant's entire argument ignores the claim phrase "and/or the apyrase". The use of the term "or", when properly interpreting the claim, clearly indicates that apyrase represents an alternative to pyrophosphatase that is expressly stated in the claim. So

when Nyren (WO 98/13523) teaches addition of apyrase, followed by removal of apyrase, Nyren (WO 98/13523) is anticipating claim 1.

With regard to the prima facie obviousness rejection, once Nyren (WO 98/13523) teaches removal of ATP in the substrate solution using apyrase prior to analysis followed by removal of the enzyme along with the separate teaching by Nyren (WO 98/28440) that Ppi is also a problem and should be removed along with the pyrophosphatase enzyme, an ordinary practitioner would have been motivated to combine these teachings for the reasons given in the rejection. Applicant points to no secondary consideration or other reason why the rejection should fall. Therefore, Applicant's argument is not persuasive.

Conclusion

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jeffrey Fredman
Primary Examiner
Art Unit 1637
9/11/06